antibodies to human Ig and the specific binding of [the] said labeled antibodies to [the] said washed support is measured.

65. (Amended) The method of claim 64 wherein [the] said labeled antibodies bound to [the] said washed support are measured by an enzyme label.

66. (Amended) An article of manufacture adapted for use in an immunoassay for antibodies to an human immunodeficiency virus (HIV) comprising a solid support having bound thereto a synthetic HIV polypeptide comprising at least an [immunogenic] antigenic portion of the envelope (env) domain of HIV.

REMARKS

The Present Invention

The present invention is directed to an immunoassay for the detection of HIV in a clinical sample using synthetic envelope polypeptides. Embodiments of the present invention include an article of manufacture by which the immunoassay is performed.

Amendments to the Claims

Claims 60-66 have been amended to clarify better the subject matter. All of the amended claims recited or referred back to an "immunogenic polypeptide," which has been deleted due to the section 112 objection recited in the Office Action. A clearer term used instead is an --antigen,-- which is

supported in the present specification at p. 26, l. 15 and in the specification of Ser. No. 06/667,501 at p. 14, ll. 21-36. No new matter has been added by way of the above-recited amendments.

The Present Claims

Claims 60-66 are pending in the present application. Claims 60-65 are directed to a method of detecting antibodies to a human immunodeficiency virus (HIV). Claim 66 is directed to an article of manufacture adapted for use in an immunoassay for antibodies to HIV.

The Office Action

The Office Action of June 22, 1994 rejected the claims of the present application as follows:

(1) Claims 60-66 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach adequately how to make and/or use the invention;

(2) Claims 60-66 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter that applicants regard as the invention; and

(3) Claims 60-66 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chang et al. (U.S. Patent 4,774,175; filed March 1, 1985) or Cosand et al. (U.S. Patent 4,629,783; filed August 19, 1985).

The Inventors' Declaration

The Office Action notes that the Declaration dated August 17, 1992, currently in the Patent and Trademark Office's file of the present application is defective. Applicants accordingly have attached hereto a new and complete copy of the Declaration and respectfully request that it replace the defective copy.

Discussion Of The Rejection Under Obviousness-Type Double Patenting

The Office Action recites that claims 60-66 stand rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-22 of U.S. Patent 5,156,949, which matured from the grandparent application of the present application. Both applications (and the resultant patent) are commonly owned.

Applicants respectfully disagree that the claims of the present application are obvious in any manner in view of any published reference, including the recited grandparental patent. However, in the interest of expediently attaining patent coverage directed to the pending claims, applicants, through their attorneys, offer to file a terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) with respect to the term of the '949 patent, prior to issuance of any allowed claims of the present invention.

Discussion Of The Rejection Under
35 U.S.C. § 112, First Paragraph

Claims 60-66 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach adequately how to make and/or use the invention. Applicants respectfully traverse, as follows:

The Office Action recites that deposit of the "expression plasmid containing the KpnI-EcoR1 fragment or the starting lambda clone would satisfy the enablement requirements of 35 U.S.C. § 112" (Office Action at p. 4, ll. 16-18). The Office Action also recites that such a deposit is required to establish the enablement of the ancestral parent application, namely Ser. No. 06/667,501 (filed October 31, 1984; hereinafter, "the '501 application"). In fact, a lambda clone that includes the recited fragment has been deposited by applicants. As recited in the present specification at p. 157, l. 15, λ-ARV-2(9B) was deposited January 25, 1985, under the provisions of the Budapest Treaty with the American Type Culture Collection in Rockville, MD, and has ATCC Accession No. 40158. As recited at p. 38, ll. 31-32, "λ-9B contained an insertion of full-length proviral DNA." Because any artisan of ordinary skill can obtain the recited fragment from, for example, the λ-ARV-2(9B) clone without need to resort to undue experimentation, applicants respectfully submit that this objection and rejection should be withdrawn.

The Office Action alleges that the present invention fails to enable the recited claims or provide adequate description

thereof with respect to (1) identifying and producing immunogenic portions [i.e., epitopes] of the envelope domain [that] contribute to its immunogenicity [or antigenicity]" (Office Action at p. 3, ll. 8-10 and 13-14), and (2) "how to produce the claimed immunogenic polypeptides by chemical synthesis" (Office Action at p. 6, l. 12).

The Office Action also alleges that the ancestral parent of the present application, namely the '501 application, fails to enable the recited claims or provide adequate description thereof with respect to (3) "guidance as to how to prepare the expressed protein for use in other immunoassay formats" (Office Action at p. 3, l. 23 to p. 4, l. 1), (4) "characterization of the expressed product" (Office Action at p. 4, l. 1), (5) description of "expressed material ... [as] envelope domains in as much as the insert contains sequences additional to the putative envelope gene" (Office Action at p. 4, ll. 3-5), and (6) "modifications to the KpnI-EcoR1 fragment ... to facilitate expression in other eukaryotic or prokaryotic expression systems" (Office Action at p. 4, ll. 6-7).

The Office Action further alleges that the grandparent of the present application, namely Ser. No. 07/138,894 (filed December 24, 1987; matured into U.S. Patent 5,156,949; hereinafter, "the '949 patent"), fails to enable the recited claims or provide adequate description thereof with respect to (7) "what sub-regions of the expressed domains ... have a reasonable expectation of being [antigens to] antibodies

present in the sera of patients infected with HIV" (Office Action at p. 5, ll. 24-26).

In response to the assertions of the Office Action that the present and/or ancestral applications inadequately enable or describe the recited claims, applicants respectfully submit, in contrast, that one skilled in the art using conventional knowledge would be able to comprehend and apply the teachings of the present invention such that each of the aforementioned objections (numbered hereinabove 1 through 9) is moot. For example, all procedures necessary for the above methods, identifications, characterizations, syntheses, etc. would require, at most, the application of conventional techniques and routine screening. The procedures for such conventional techniques and routine screenings are well known in the art as recited in, for example, Maniatis et al., Molecular Cloning: A Laboratory Manual (Cold Spring Harbor, New York, 1982) and many other publications that date prior to October 31, 1984. As is well established in the patent law, routine screening does not obviate the enablement of an invention. See In re Ward, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) ("The test [of whether experimentation precludes enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine....").

The present specification, as well as those of the '501 application and '949 patent, provides adequate support for claims 60-66 as amended because "[a] specification may, within the meaning of 35 U.S.C. § 112, ¶1, contain a written descrip-

tion of a broadly claimed invention without describing all species [or provide detailed guidance for obtaining same] that claim encompasses." Utter v. Hiraga, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988). After all, "a patent need not teach, and preferably omits, what is well known in the art." Hybritech Incorporated v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

Moreover, applicants respectfully submit that adequate guidance for the present invention, as understood by one of ordinary skill in the art, is set forth in the present and '501 applications and '949 patent, as detailed hereinbelow.

Methods are provided in the present specification for identifying portions of the envelope domain that are immunogenic (at pp. 125-126, 129-131, 134-137, and 152-153). Moreover, other methods well-known in the art for the identification of epitopes are known in the art, such as Geysen et al., Biochemistry, 81, 3998-4002 (July 1984). Methods for producing such immunogenic portions of envelope domain is set forth in the specification at, for example, pages 24-26, and exemplified in the specification at, for example, pages 45-47, 76-79, and 86-90.

Chemical synthesis for the production of the claimed antigens is noted in the present specification at, for example, page 5, lines 3-4. Methods for linking one amino acid to another in a directed fashion, thereby producing a synthetic polypeptide, are well known in the art, as evidenced by, for example, Merrifield, J. Am. Chem. Soc., 85, 2149-2154 (1963)

and Spatola in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7, pp. 267-357 (B. Weinstein, ed., Decker, New York, 1983). Moreover, the applicants contemplate the present invention as providing novel variants of the disclosed envelope domain polypeptides by way of modifying the DNA sequence that encodes it. Such methods are known in the art and are noted in the specification at, for example, pages 61 and 70.

Methods for preparation of the expressed protein for use in other immunoassay formats is set forth in the '501 application at, for example, pages 10-11 and 13. Moreover, methods known in the art for such modification are readily available in Maniatis et al. (supra). Characterization of the expressed product, and isolation thereof, is discussed in the specification at pages 13-14, for example. Methods for such characterization of expressed gene products are known in the art, as evidenced by standard biochemistry texts, including Lehninger, Biochemistry (Worth Publishers, New York, 1970).

With respect to the Office Action's questioning at page 4, lines 3-5, as to whether the COS cells transformed with the KpnI-EcoR1 fragment expresses envelope polypeptides, applicants respectfully submit that conventional analysis using immunofluorescence where the antibody is directed to envelope antigens has clearly demonstrated the production of envelope polypeptides in so transformed COS cells. No such production has been demonstrated in non-transformed COS cells. Accordingly, the present invention is fully disclosed in the '501 application

in view of the inherent characteristic of COS cells transformed with the KpnI-EcoRI fragment to produce envelope polypeptides.

The '501 specification also clearly sets forth methods for modifying the KpnI-EcoRI fragment to facilitate expression of the desired polypeptide. At page 13, the '501 specification recites that the sequence for expression "may be manipulated ... by employing restriction endonuclease digestion, primer repair, in vitro mutagenesis, ligation of fragments, [and/or] exonuclease digestion." These techniques and more are set forth in Maniatis et al. (supra) and can be implemented by a routineer.

With respect to whether the '949 patent enables the identification of antigenic sub-regions of the expressed domains, applicants respectfully submit that such a method is well-known in the art as exemplified by Geysen et al., supra. Moreover, the '949 patent sets forth methods to generate envelope sub-region polypeptides (see col. 42, l. 55 to col. 43, l. 48) and to test such resultant polypeptides for immunological activity (see col. 61, l. 44 to col. 67, l. 62), for example. Results of such studies are set forth at, for example, col. 67, l. 63 to col. 72, l. 41.

In view of the above, applicants respectfully request that the section 112, first paragraph, be withdrawn.

Discussion Of The Rejection Under
35 U.S.C. § 112, Second Paragraph

Claims 60-66 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out particularly and claim distinctly the subject matter that applicants regard as the invention. In particular, the Office Action alleged that the phrase "immunogenic polypeptide" in the context of the present invention is confusing. Applicants have removed all recitation of this phrase and substituted therefor --antigen--. As noted above, the new phrase is fully supported by the specification at, for example, p. 26, l. 15. The Office Action also objected to the recitation of "synthetic polypeptide" as being indefinite. Applicants respectfully submit that such is not the case, that the term synthetic polypeptide is generally known in the art as a polypeptide generated by chemical means. Such chemical means is distinguished readily from biological means for generating a polypeptide, such as by recombinant technology. See, e.g., King, A Dictionary of Genetics (Oxford University Press, 1972) at p.281. In King, "synthetic polyribonucleotides" is defined as "RNA molecules made without a nucleic acid template, by either enzymatic action or chemical synthesis in the laboratory." By analogy, and certainly well understood by those of ordinary skill in the art, a synthetic polypeptide is a polypeptide made by chemical synthesis without a nucleic acid template. Applicants have incorporated the suggestion of the Office Action and have amended the claims to recite the claimed polypeptide as an HIV

polypeptide. Accordingly, applicants respectfully submit that the section 112, second paragraph rejection should be withdrawn.

Discussion Of The Rejection Under 35 U.S.C. § 102(b)

Claims 60-66 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chang et al. (U.S. Patent 4,774,175; filing date March 1, 1985) or Cosand et al. (U.S. Patent 4,629,783; filed August 19, 1985; matured from a continuation-in-part of Serial No. 728,052, filed April 29, 1985). Because neither of these references predate the priority date of the present application, that being October 31, 1984, applicants respectfully submit that the anticipation rejection should be withdrawn. Accordingly, the section 102(b) rejection is moot.

Conclusion

In view of the above amendments and remarks, the application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (312) 616-5600.

Respectfully submitted,

By _____

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In re LUCIW et al.
Serial No. 08/089,407

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